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Reply to the letter comment of Su Boon Yong MD, PhD and colleagues to: Improved glycemic and weight control with Dulaglutide addition in SGLT2 inhibitor treated obese type 2 diabetic patients at high cardiovascular risk in a real-world setting. The AWARE— 2 study

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Dear Su Boon Yong MD, PhD and Colleagues

Thank you for your interest in our work, and we are very grateful for your stimulating considerations and suggestions. We are responding to your letter in a point-by-point fashion, in order to facilitate readers comprehension.

1) We agree that body composition analysis is an important aspect in the qualitative assessment of weight loss. Indeed, it allows monitoring of both muscle and lean tissue loss thus possibly avoiding the risk of sarcopenia and associated reduced muscle strength and altered muscle protein synthesis and degradation. Gold standard techniques for monitoring the quali-quantitative aspect of weight loss are dual-energy X-ray absorptiometry (DXA) or bioimpedance analysis (BIA) [1]. Our study is a real world analysis with data collected retrospectively from hospital centers and territorial outpatient clinics [2]. In this setting, DEXA and BIA could not be performed and did not have any indication in the treatment and follow up of diabetic patients. It is well known that even in the RCTs study of the AWARD program which investigated the effect of dulaglutide in addition to SGLT2i, diabetic patients were enrolled on also the basis of BMI and weight loss was assessed only in terms of weight reduction [3]. Moreover, our study primary end point to evaluate the efficacy of the association of SGLT-2 inhibitors and GLP1 receptor agonists on metabolic control (HbA1c) and body weight in a real world setting [4–6]. In any case, body composition assessment during weight loss is clinically important, and the suggestion to use more sensitive tools in future research is correct and welcomed.
2) We agree that weight regain and dropping out of therapy are two key aspects in the follow-up of subjects with weight loss also in obese population without type 2 diabetes. In our population, weight loss is probably accompanied by reduction in insulin resistance and cardiovascular risk. In clinical practice in type 2 diabetes, it is not strictly necessary to evaluate weight regain after interruption of treatment with GLP-RA. As a matter of fact, weight regain is not only observed after a variety of pharmacological therapies including GLP1-RA, but also it happens after bariatric surgeries [5]. In our study, we verified the use of AWARE App to classify patients according to different risk classes and [7] the short follow-up of 6 months did not allow us to evaluate a possible weight regain, and this was not a secondary end-point.
3) The limitations of our study are specified in the manuscript [2]. Data collection at baseline and follow-up was done employing a specific APP (AWARE app) [7] to record in real-time bioanthrometric data necessary to stratify patients' cardiovascular risk, according to the ESC-EASD 2019 Guidelines [8] and to initiate/modify hypoglycemic therapies based on the risk class at baseline. The AWARE app allowed us to record therapies, at baseline and after 6 months of follow-up. At the end of the study period (6 months), with the exception of metformin use which remained quite constant, the addition of dulaglutide resulted in major reductions of all other concomitant hypoglycemic therapies including insulin. These findings strongly suggest that HbA1c and weight reductions depend mainly on the addition of Dulaglutide, and also to significant reductions in the use of insulin, insulin secretagogues and pioglitazone [2]. All patients with type 2 diabetes participants (and all patients in this study) are subjected to educational therapy by nurses and dieticians, aimed at teaching appropriate lifestyles and diets for the management of diabetes.

CRediT authorship contribution statement

Cesare Berra: Writing – review & editing. **Manfrini Roberto:** Writing – review & editing. **Bifari Francesco:** Writing – original draft. **Cipponeri Elisa:** Writing – original draft. **Ghelardi Renata:** Writing – original draft. **Centofanti Lucia:** Writing – original draft. **Mortola Umberto:** Writing – original draft. **Lunati Elena:** Writing – original draft. **Bucciarelli Loredana:** Writing – original draft. **Cimino Vincenzo:** Writing – original draft. **Folli Franco:** Writing – review & editing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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